

The metabolic syndrome and cardiovascular disease: the CODAM study

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7.1. The CODAM Study

The primary aims of the Cohort on Diabetes and Atherosclerosis Maastricht (CODAM) study are to evaluate the progression of atherosclerosis and cardiovascular disease (CVD) in subjects with a relatively high risk of type 2 diabetes mellitus (T2DM) and to evaluate the development of T2DM in subjects who were selected for specific T2DM risk factors. To be able to study these questions the cohort will be seen every 7 years to assure a regular follow-up. This thesis focused on the first primary aim. Since only the baseline measurements of this cohort were available by the time the investigations described in this thesis were done, data from cross-sectional analyses are presented.

7.2. The metabolic syndrome in CODAM

Presence of the metabolic syndrome is a “common denominator” in subjects with high risk of CVD and T2DM [1-4]. The metabolic syndrome defines a clustering of risk factors including abdominal obesity, hypertension, elevated plasma triglyceride concentration, reduced high-density lipoprotein (HDL)-cholesterol concentration and elevated fasting blood glucose levels [5, 6]. Given the selection criteria for the CODAM study, the metabolic syndrome was likely to be a frequent finding in CODAM participants. Prevalence of the metabolic syndrome according to national cholesterol education program 2005 [7] was in subjects with normal glucose tolerance 33.2%, with impaired glucose metabolism 69.3% and, with T2DM 86.3% in the CODAM participants. Cross-sectional and prospective studies have shown that the metabolic syndrome is associated with CVD and that people with the metabolic syndrome have an increased risk for future CVD [8-11]. However the exact mechanisms that might explain this association are not entirely clear. Therefore we investigated cross-sectionally which mechanisms/processes might underlie the association between the metabolic syndrome and CVD [12-14]. In these investigations we focused on several metabolic markers and potential intermediates that are of specific interest in the relation between the metabolic syndrome and CVD, including insulin resistance, inflammation, endothelial dysfunction, complement C3 and non-alcoholic fatty liver disease (NAFLD).

7.3. Central and peripheral artery disease in CODAM

7.3.1. The metabolic syndrome and coronary and peripheral artery disease

We first set out to investigate how the association between the metabolic syndrome and different aspects of cardiovascular disease were affected by intermediate processes

in CVD, i.e. inflammation and endothelial dysfunction. In these investigations we specifically focused on two distinct aspect of CVD i.e. the coronary and the peripheral vasculature, since these are two different vascular beds that might be affected in a different manner by the metabolic syndrome.

We showed that low-grade inflammation explained, statistically, part of the association between the metabolic syndrome and coronary artery disease (CAD) (up to 26%) and the severity of peripheral artery disease (PAD) (up to 29%, Chapter 2). The most studied marker of systemic low-grade inflammation in association with the metabolic syndrome and CVD is C-reactive protein [15, 16]. However, more markers of inflammation exist, including interleukin 6, soluble intercellular adhesion molecules, soluble vascular cell adhesion molecules and serum amyloid A. These have been investigated before [15, 17-19], but only as separate markers. In our investigations we combined several inflammatory markers into a composed score that represented systemic low-grade inflammation what is a more robust measure for inflammation than the markers separately with the additional advantage of less misclassification [20]. Since the association between the metabolic syndrome and CAD and the severity of PAD was only partly explained by inflammation we subsequently investigated (Chapter 3) whether endothelial dysfunction could explain an additional part of this association. As a measure for endothelial dysfunction we also used a robust measure of biomarkers that were combined into an endothelial dysfunction score [20]. We found that endothelial dysfunction explained about 19% of the association between the metabolic syndrome and the severity of PAD, low-grade inflammation explained 28%. Together endothelial dysfunction and low-grade inflammation explained 36%, so 8% was additional to low-grade inflammation (Figure 7.1). This implies that inflammation and endothelial dysfunction partly represent the same pathway in the relation between the metabolic syndrome and PAD but can have individual contributions as well. On the other hand, endothelial dysfunction did not explain any part of the association between the metabolic syndrome and CAD. Together with the former this shows that the pathogenesis of peripheral and coronary artery disease differ in this respect. It could be argued that it would have been better to use functional measure of endothelial dysfunction, like flow-mediated dilatation instead of biomarkers [21]. However compared to such a more direct measure of endothelial function, the use of biomarkers would only underestimate our findings which make our results unlikely to be a spurious finding.

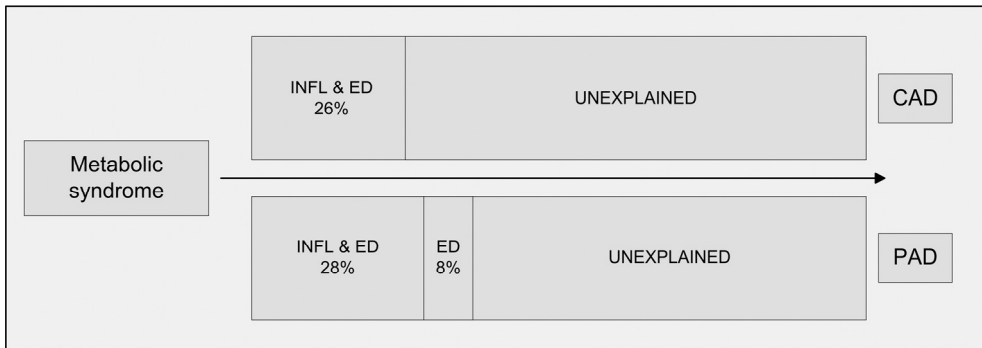


Figure 7.1: The association between the metabolic syndrome and coronary artery disease (CAD) and peripheral artery disease (PAD), adjusted for age, sex and lifetime smoking, is partly mediated by inflammation (INFL) and endothelial dysfunction (ED)

7.3.2. The complement system and coronary heart disease

The complement factor C3 has been established as a cardiovascular risk factor in both cross-sectional and longitudinal studies [22, 23] and is substantially increased in the circulation of subjects with the metabolic syndrome [24].

In the CODAM population (Chapter 4), we confirmed that human serum complement factor C3 was indeed cross-sectionally associated with coronary heart disease (CHD) as was previously shown by others [25-27]. However, based on previous *in vitro* data that cigarette smoke can activate the complement system by modifying complement C3 [28-30] we hypothesized that smoking may enhance the effect of complement of the risk of CVD. Indeed, closer examination of the association between complement C3 and CHD learned that this was mainly present in the group of heavy smokers. This association was independent of cardiometabolic risk factors like insulin resistance, systemic inflammation and the metabolic syndrome. The overall association of C3 with CHD we found in the whole CODAM population corresponds with the associations between C3 and prevalence of CHD, independent of age, sex and some additional risk factors reported by several other studies [23, 25, 31, 32]. There are several possible explanations how smoking might increase the risk of CVD associated with C3 in these cross-sectional evaluations. A first explanation is that the activation of complement C3 by (heavy) smoking might be one of the mechanisms by which smoking can enhance the process of inflammation in the atherosclerotic plaque and thereby increasing the risk of CVD. Another possibility is that smoking would not directly affect the complement system but rather induce oxidative stress and inflammation in the atherosclerotic plaque, which might affect the expression and/or activation of the complement system.

7.4. Metabolic risk factors in CODAM

7.4.1. The metabolic syndrome and non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease is a highly prevalent finding (70% to 80%) in subjects with the metabolic syndrome [33, 34] and has a wide histological spectrum ranging from simple steatosis and non-alcoholic steatohepatitis to more progressive forms such as fibrosis and eventually cirrhosis. Alanine aminotransferase (ALT) in the circulation is a simple measure for fatty liver disease. Several metabolic syndrome-related processes might affect the development of NAFLD.

We showed in Chapter 5 that insulin resistance was, statistically, the strongest mediator of the association between the metabolic syndrome and ALT while other metabolic syndrome related processes like inflammatory adipokines, endothelial dysfunction and non-esterified fatty acids (NEFA) also explained a part of the association, but to a lesser extent, Figure 7.2. The strong mediation by insulin resistance was not really surprising because of well-known relations between the metabolic syndrome, insulin resistance and steatosis [35]. The mediation by inflammatory adipokines and endothelial dysfunction did not add to the mediation by insulin resistance, which implies that these processes overlap and supports the notion that -in the metabolic syndrome- insulin resistance-associated adipose tissue inflammation and endothelial dysfunction might actually contribute to the development and/or progression of NAFLD, as reflected by ALT. NEFA on the other hand did add to the mediation by insulin resistance; about half of the mediation by NEFA was additional to insulin resistance. This suggests that half of the mediation by NEFA may occur via pathways included in the process of adipose tissue inflammation and insulin signaling, while the other half occurs via other processes like dietary fatty acids and direct uptake by hepatocytes of adipose tissue derived NEFA.

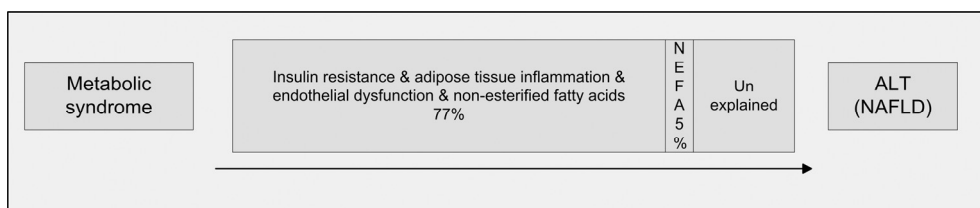


Figure 7.2: The association between the metabolic syndrome and non-alcoholic fatty liver disease (NAFLD; measured as ALT), adjusted for age, sex, smoking, alcohol consumption and the use of lipid-lowering and anti-hypertensive medication, is for a very large part mediated by insulin resistance, with no independent contribution of adipose tissue inflammation, endothelial dysfunction. The mediation by non-esterified fatty acids (NEFA) is partly independent of insulin resistance

7.4.2. Fatty liver as an intermediate in the relation between insulin resistance and complement C3

As described above (paragraph 7.3.2), increased levels of circulating complement C3 are a frequent finding in subjects with the metabolic syndrome. Several aspects of the metabolic syndrome, including insulin resistance, may contribute to increased amounts of circulating complement factor C3.

In the CODAM population, insulin resistance was, as expected based on literature [36, 37], indeed associated with circulating concentrations of complement C3. We now showed that NAFLD, measured by ALT, partly explained this association, independent of obesity and low-grade inflammation (Chapter 6). Given the substantial production of C3 by the liver, the observed 14% mediation appeared, at first sight, to be quite low. However estimations of the contribution of the liver to systemic C3 are primarily based on data from subjects who received a liver transplantation [38] and such individuals can metabolically not be compared to the subjects in the CODAM study. Moreover, we did not study the association between ALT and circulating C3 but evaluated to what extent ALT could explain the association between C3 and insulin resistance.

Taking all the above together, our studies showed that several processes explain part of the association between the metabolic syndrome and (metabolic intermediates of) cardiovascular disease. These processes include low-grade inflammation, insulin resistance, endothelial dysfunction, complement and non-esterified fatty acids, but our investigations showed that these processes overall are partly overlapping and partly independent from each other.

7.5. Methodological considerations

7.5.1. Internal validity

In the manuscripts presented in this thesis, we have used a range of biomarkers as proxy measures of general inflammation, adipose tissue inflammation and endothelial dysfunction. Different sets of markers were combined into scores to obtain more robust measures of these above-mentioned processes with the benefit of less misclassification and reduction of the problem of multiple testing. An important advantage of the use of biomarkers is that they are relatively easy obtainable in large epidemiological cohorts. A disadvantage might be that they are estimates of underlying (patho-)physiological processes but do not directly measure them.

We have used several markers for low-grade inflammation and made a distinction between general and adipose tissue-related low-grade inflammation. C-reactive protein

is a marker for inflammation that is mostly produced by the liver and therefore a marker for general inflammation. Adiponectin and leptin on the other hand are markers that are exclusively produced by adipocytes and therefore representative for adipose-tissue related inflammation. The other markers we used (i.e. IL6, sICAM, SAA) are not unique produced in one cell type. So it is more difficult for these markers to assign them to a specific type of inflammation and therefore it is possible that both inflammation scores include markers that are not unique for that score.

We also used biomarkers to estimate endothelial dysfunction. Functional measures for endothelial function have been used in other studies, however until now there is not a gold standard to measure endothelial dysfunction. The most used functional measure is endothelium-dependent flow-mediated vasodilatation. Unfortunately, this measure was not available. By using a combined score for endothelial dysfunction instead of one or more individual markers we, again, tried to reduce the problem of misclassification and multiple testing.

The gold standard for diagnosing and staging NAFLD is a liver biopsy. This is an invasive procedure with risk of postinterventional bleeding and is therefore ethically not acceptable without clinical indication. Other techniques that are frequently used in epidemiological studies include imaging techniques like ultrasound or by measurement of circulating markers such as alanine-aminotransferase. However, previous studies have shown that ALT is a reasonable predictor of NAFLD as detected by ultrasound [39, 40].

Coronary artery disease was defined as self-reported myocardial infarction, bypass surgery of the coronary arteries, balloon dilatation or stent placement (through questionnaires) and/or the presence of signs of myocardial infarction or ischemia on a 12-lead electrocardiogram. For more than 75% of the subjects, the self-reported CAD could be confirmed using available hospital registries. The ankle-arm index was measured for PAD, the most used method. Since only 28 of 574 subjects had an ankle-arm index (AAIx) < 0.9 (the traditional criterion to define PAD), we lacked power to use PAD as a categorical variable and we therefore used the AAIx as a continuous measure for the severity of PAD.

7.5.2. External validity

Subjects who were selected into CODAM had a relatively high risk of T2DM and CVD. Generalizability of our current data is therefore restricted to subjects who have a comparable risk profile of obesity, (slightly) disturbed glucose metabolism and/or high blood pressure. Subjects who fulfill these criteria are present in our Western society with a high prevalence and they are the ones who have the highest risk to develop cardiovascular and/or macrovascular complications. The data presented in this thesis can largely be generalized to those high-risk subjects and these data contribute to our understanding of development of disease in this particular group of

subjects. We should, however, be cautious with generalization of our results to high-risk subjects of different ethnicity or of (much) younger age, since these were not included in our cohort.

For more generalizable data, our investigations should be repeated in other populations.

All studies presented in this thesis were done cross-sectionally which precludes conclusions on causality.

7.6. Future research within CODAM

From 2005 until 2009 all participants of the CODAM baseline measurement were invited to participate in the first follow-up evaluation (CODAM 2). Of the original 574 participants, 491 (>85%) visited our laboratory twice for these 7 years follow-up evaluations. During these visits all measurements that were performed during CODAM 1 were repeated to assure that longitudinal analysis can be performed.

During the first visit anthropometric measures were taken (length, weight, waist and hip circumference, skin-fold measures) and blood pressure was measured in both arms in sitting and in supine position. Besides in the arms, blood pressure was also measured in both legs, to be able to calculate the ankle-arm index. In supine position also an ECG was taken so signs of CAD could be recognized. Then fasting blood samples were taken to measure markers like among others glucose, HDL-cholesterol, triglycerides, markers of low-grade inflammation, complement C3 and endothelial dysfunction. To define whether the participants had T2DM we performed an oral glucose tolerance test, during which the participants completed the same questionnaires as were filled in during CODAM 1.

The second visit was mainly used to perform vascular measurements and additional measurements on body composition and fat distribution. Ultrasound was used to measure intima-media thickness in both carotid arteries. Also the distension was measured in both carotid arteries as well as in the brachial and femoral arteries, as a measure of stiffness. Other measures of stiffness were the augmentation index and pulse wave velocity (central: carotid artery – femoral artery and peripheral: femoral artery – ankle). Since in CODAM 1 we only had the biomarker ALT as a measure for NAFLD, we now used ultrasound to have a more direct/better measure for fatty liver disease. Finally an intravenous glucose tolerance test was done.

With the results of CODAM 2 together with those of CODAM 1, we will be able to study various aspects and causes of the development and progression of T2DM, atherosclerosis and CVD in these high-risk subjects.

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Samenvatting

Het metabool syndroom is een verschijnsel dat vaak voorkomt bij mensen met een hoog risico op type 2 diabetes mellitus en hart- en vaatziekten en is een cluster van risicofactoren, waaronder abdominale obesitas, hoge bloeddruk, verhoogde concentratie van triglyceriden en verlaagde concentratie van HDL-cholesterol in het bloed en verhoogde bloedglucose waarden. Als gevolg van de selectiecriteria die gebruikt zijn om te komen tot onze onderzoekspopulatie (Cohort Onderzoek naar Diabetes en Atherosclerose Maastricht; CODAM), werd het metabool syndroom vaak gevonden bij de deelnemers. Het metabool syndroom kwam bij 33.2% voor van de personen met een normale glucose tolerantie, bij 69.3% van de personen met een verminderde glucose tolerantie en 86.3% bij personen met type 2 diabetes.

Diverse andere studies hebben al aangetoond dat het metabool syndroom geassocieerd is met hart- en vaatziekten en dat personen met het metabool syndroom ook een verhoogd risico hebben op hart- en vaatziekten in de toekomst. De precieze mechanismen die deze associatie kunnen verklaren zijn nog niet bekend. Daarom hebben wij gekeken naar de mechanismen/processen die hier aan ten grondslag kunnen liggen en hebben ons hierbij gefocust op insuline resistentie, ontsteking, endotheel dysfunctie, complement C3 en niet-alcoholische leververvetting.

In hoofdstuk 2 en 3 hebben we gekeken naar de associatie van het metabool syndroom met hart- en vaatziekten en hoe deze mogelijk verklaard kan worden. We hebben ons gefocussed op twee verschillende aspecten van hart- en vaatziekten, namelijk coronair vaatlijden en perifeer vaatlijden omdat deze twee vaatbedden waarschijnlijk op een andere manier door het metabool syndroom beïnvloed worden.

We laten in hoofdstuk 2 zien dat laaggradige ontsteking statistisch gezien een deel kan verklaren van de associatie die gevonden is tussen het metabool syndroom en coronair vaatlijden (tot 26%) en van de associatie tussen het metabool syndroom en de ernst van perifeer vaatlijden (tot wel 29%). Diverse markers die in het bloed gemeten kunnen worden geven een maat voor laaggradige ontsteking, maar er is niet één marker die 'uniek' is. Daarom hebben we in ons onderzoek meerdere markers gebruikt voor het berekenen van een gecombineerde score die representatief is voor algehele laaggradige ontsteking. Deze score is een robuustere maat voor ontsteking dan de afzonderlijke markers met tevens het voordeel dat de kans op misclassificatie veel kleiner is.

Aangezien laaggradige ontsteking de associatie tussen het metabool syndroom en verschillende aspecten van hart- en vaatziekten slechts voor een deel kan verklaren hebben we in hoofdstuk 3 gekeken of endotheel dysfunctie een extra deel van deze associatie kan verklaren. Voor endotheel dysfunctie hebben we, net als voor laaggradige ontsteking, een gecombineerde score berekend van diverse markers. Endotheel dysfunctie kon 19% en laaggradige ontsteking 28% van de associatie tussen het metabool syndroom en de ernst van perifeer vaatlijden verklaren. Samen

verklaarden ze 36%, dus endotheel dysfunctie voegde 8% toe aan de verklaring die gevonden werd door laaggradige ontsteking. Het lijkt er dus op dat laaggradige ontsteking en endotheel dysfunctie deels dezelfde route representeren, maar ook ieder hun eigen bijdrage hebben. Verder bleek dat endotheel dysfunctie niets verklaard van de associatie tussen het metabool syndroom en coronair vaatlijden. Dit laat, samen met het voorgaande, zien dat de pathogenese van perifeer en coronair vaatlijden verschillend is.

In hoofdstuk 4 hebben we laten zien dat complement C3 cross-sectioneel geassocieerd is met coronair vaatlijden. Dit hebben we uitgebreider bekeken en zagen dat deze associatie voornamelijk naar voren kwam in de groep personen die veel rookt, onafhankelijk van cardiometabole risicofactoren zoals insuline resistentie, laaggradige ontsteking en het metabool syndroom.

Niet-alcoholische leververvetting in verschillende gradaties wordt vaak gezien bij mensen met het metabool syndroom. Omdat leververvetting niet heel eenvoudig vastgesteld kan worden, hebben wij daarvoor de niveaus van alanine aminotransferase (ALT) in het bloed bepaald wat een vereenvoudigde maat is voor niet-alcoholische leververvetting. We laten in hoofdstuk 5 zien dat insuline resistentie de grootste verklaring gaf voor de associatie tussen het metabool syndroom en ALT. Andere processen die gerelateerd zijn aan het metabool syndroom verklaarden ook een deel van de associatie, maar waren niet zo sterk. Ontstekingsmarkers afkomstig uit vetcellen voegden niets toe aan de verklaring gevonden door insuline resistentie (77%), terwijl de helft van de verklaring door niet-geësterificeerde vetzuren (NEFA; 5%) wel extra was bovenop insuline resistentie. Dit suggereert dat de helft van de mediatie door NEFA gebeurt volgens routes die samenvallen met processen als ontsteking in het vetweefsel en insuline signalering terwijl de andere helft gebeurt volgens andere processen.

Eerder hebben we al laten zien dat een verhoogde concentratie van complement C3 in het bloed vaak gevonden wordt bij personen met het metabool syndroom. Verschillende aspecten van het metabool syndroom, inclusief insuline resistentie kunnen bijdragen aan verhoogde concentraties van C3 in het bloed. Insuline resistentie is geassocieerd met de concentratie C3 in het bloed in de CODAM populatie, zoals te zien is in hoofdstuk 6. We hebben tevens laten zien dat niet-alcoholische leververvetting, gemeten als ALT, een deel van de associatie kan verklaren, onafhankelijk van obesitas en laaggradige ontsteking.

Met alle bovenstaande bevindingen uit onze onderzoeken laten we zien dat diverse processen een deel kunnen verklaren van de associatie tussen het metabool syndroom en (metabole intermediären van) cardiovasculaire ziektes. Met de processen bedoelen

we laaggradige ontsteking, insuline resistentie, endotheel dysfunctie, complement en niet-geësterificeerde vetzuren. Verder hebben we laten zien dat deze processen deels overlappend zijn en deels onafhankelijk van elkaar.